THE UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION

Petition to Require Purdue Pharma L.P. to Revise the Labeling of OxyContin® Tablets to Strengthen Warnings of the Greater Potential for Developing Side Effects and Adverse Drug Reactions Due to Prescribing Dosing Frequencies in Excess of the Recommended Guidelines	**Docket No.** _____

Submitted by: **Richard Blumenthal**
Attorney General
State of Connecticut

January 23, 2004

CITIZEN PETITION

Richard Blumenthal, the Attorney General for the State of Connecticut ("Petitioner"), submits this Petition to request action by the Food and Drug Administration ("FDA") regarding the narcotic analgesic OxyContin® Tablets ("OxyContin"). Specifically, the undersigned requests that the Commissioner of the FDA require Purdue Pharma L.P. ("PPLP") to take various actions to expressly warn prescribers of the increased occurrence of side effects or potentially serious adverse reactions resulting from prescribing OxyContin at dosing intervals less than the manufacturer's recommended every 12 hours. The action proposed includes: strengthening the drug's "black box" warning statement, supplementing the labeling with additional bolder warnings, and initiating a "Dear Healthcare Professional" letter. In the alternative, the Petitioner asks this agency to disseminate these warnings through a Safety Alert, Public Health Advisory, Talk Paper, or Urgent Notice.

Information obtained by the Petitioner and included herein from PPLP and its internal documents, as well as from independent sources and medical experts, establishes that (1) the incidence of prescribing OxyContin at dosing intervals more frequent than the recommended every 12 hours ("q12h") has risen, on average, to approximately 20% of all prescriptions written, a practice due, at least in part, to a fundamental misunderstanding by healthcare providers of OxyContin's unique drug delivery system, which differs from the delivery systems of other opioids; (2) certain patients receiving OxyContin at intervals more frequent than q12h are more at risk of developing side effects and potentially serious adverse reactions due to the pharmacologic action of the drug; and (3) the increase in the number of doses beyond the recommended two per day increases the potential for diversion of the drug for illicit use.

This Petition is submitted pursuant to § 4 (d) of the Administrative Procedure Act, 5 U.S.C. § 553 (e), 21 C.F.R. §§ 10.20, 10.30, and pursuant to §§ 331(a) and 352(a) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. §§ 301, *et seq.*

I. INTRODUCTION

Millions of Americans suffer from pain related to disease or injury, and chronic pain is a significant health issue in American society, affecting an estimated 50 million people. In fact, pain is a primary reason people seek medical care, with some experts estimating that almost 80% of all visits to healthcare providers are related to pain.

Among the myriad of treatment options available in the United States to treat patients in pain, and the one that has grown the most in medical acceptance and popularity, is the use of opioid analgesics. Prior to the mid-1990s the long-term use of opioids was primarily limited to the treatment of cancer patients. In the mid-1990s, due, in part, to educational and research initiatives financed by the American Pain Society, American Geriatric Society, and drug manufacturers, including PPLP, the critical importance of pain management and treatment was recognized and the use of opioids was determined to be acceptable and appropriate for the treatment of nonmalignant chronic pain, *i.e.*, back pain, osteoarthritis, migraines, and postoperative pain. Now, pain is recognized as the "Fifth Vital Sign," and pain management has become a required part of all treatment plans at accredited healthcare facilities. This positive development is largely due to the implementation of new standards by the Joint Commission on Accreditation of Healthcare Organizations, an independent, not-for-profit organization that evaluates and accredits nearly 17,000 healthcare organizations and programs in the United States.

The recognition of pain as a reason for medical treatment, and the acceptance of new forms of pain treatment, have improved and enhanced the lives of countless Americans. They have given new physical and emotional comfort and opportunity to people whose quality of life is diminished by severe chronic pain.

With the growth in the healthcare community's awareness of the importance of pain management and the significant role that opioids play in treating both malignant and nonmalignant pain, the number of prescriptions for opioid analgesics predictably and dramatically increased. For example, from 1996 to 2000 the number of prescriptions dispensed for all common opioid analgesics (such as codeine, hydrocodone, morphine and hydromorphone) increased by approximately 23%[1] and the sales of all opioid analgesics in the United States increased from approximately $2.9 billion to $4.2 billion, an increase of almost 45%. In 2003, sales of opioid analgesics in the United States are estimated to be slightly more than $5 billion.

PPLP is a mid-sized pharmaceutical manufacturer engaged in research, development, production, marketing and licensing of both prescription and over-the-counter medicines and hospital products. PPLP is part of a privately held international consortia of companies operating in 18 countries, which includes Mundipharma (operating in Europe, Asia, Australia and South America), Napp Pharmaceutical Group in the U.K., and Purdue Pharma of Canada.

PPLP is recognized for its proprietary controlled-release technologies and other innovative drug delivery systems, and markets the leading oral formulation of oxycodone, OxyContin. PPLP also markets MS-Contin, a leading controlled-release version of morphine, and is expected, sometime in 2004, to launch Palladone™ Capsules, the first once-a-day oral hydromorphone preparation.

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[1] Drug Enforcement Administration, Office of Diversion Control, "*Working to Prevent the Diversion and Abuse of OxyContin,*" June 12, 2001.

OxyContin was approved for distribution by the FDA in 1995 and first marketed in 1996. The drug is a controlled-release formulation of oxycodone derived from the opium alkaloid, thebaine, and, at the time of its launch, was indicated for the management of "moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days." Unlike Percocet or Percodan, which are short-acting opioid combination analgesics usually administered every 4 to 6 hours, OxyContin was developed and approved as a controlled-release formulation intended to deliver a consistent level of pain relief over a 12 hour period. It is the opinion of many healthcare practitioners in the pain management area that controlled-release analgesics provide stable pain relief for the patient and avoid the peaks and troughs in the relief and pain cycle often associated with the shorter acting drugs. OxyContin is currently approved in 10mg, 20mg, 40mg, 80mg and 160mg tablet strengths.[2] When prescribed and used correctly in accordance with approved manufacturer and FDA guidelines, OxyContin is widely regarded as an effective tool in managing moderate to severe chronic pain around-the-clock for an extended period of time.

As OxyContin sales increased dramatically[3], so did the abuse and diversion of the drug. The illicit market for OxyContin stems, in large part, from the ability of addicts or abusers to circumvent the drug's controlled-release formulation by crushing and chewing the tablet, or by

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[2] PPLP has voluntarily withdrawn the 160mg strength tablet from the market due to concerns of overdose resulting from illicit use. While OxyContin is presently the only controlled-release oxycodone painkiller available for use in the United States, there are other controlled-release opioid analgesics containing different opioids that are available for pain management and which compete with OxyContin. Among the other controlled-release opioid analgesics that compete with OxyContin are: MS-Contin (Purdue Pharma), Oramorph SR (Elan), Avinza (Ligand), Duragesic (Janssen), and at least one generic controlled-release morphine product (Endo). In light of a recent federal court decision, it is likely that a generic version of OxyContin will be introduced at some point in 2004. *See Purdue Pharma L.P., et al. v. Endo Pharmaceuticals, Inc.*, Ruling, (S.D.N.Y., Jan. 5, 2004) (Stein, USDJ).

[3] According to the Drug Enforcement Administration, prescriptions for OxyContin during the years 1996 through 2000 increased by 1,800%. Drug Enforcement Administration, Office of Diversion Control, "*Working to Prevent the Diversion and Abuse of OxyContin*," June 12, 2001.

dissolving it in water and injecting it, thereby releasing all the oxycodone in the tablet into the bloodstream at once, causing what is commonly described as a "heroin-like high."

In April 2001, in response to escalating reports of abuse, diversion and potential misuse of OxyContin, and in an effort to stem these concerns, the FDA met with PPLP executives to address these developments, as well as the agency's belief that "doctors did not have the right perception about the use of OxyContin . . . that prescribing behavior is too casual," the consequence of this trend being that "prescribing of OxyContin is creeping into a whole population of people where it doesn't belong."[4] During the meeting, an FDA official suggested that PPLP needed a new educational and marketing message that "discloses the risks" and "does not promote off-label use . . . " since the "danger is not conveyed very strongly" in the promotional materials.[5] As a result, in July 2001 the drug's indication was revised to "the management of moderate to severe pain when a continuous around-the-clock opioid is needed for an extended period of time." Additional revisions and strengthened warnings to the OxyContin labeling included a "black box" warning advising patients and prescribers, among other things: (i) that the drug should not be crushed, chewed or broken due to the potential for a rapid release and absorption of a "fatal dose" of oxycodone, (ii) that it is not intended for PRN use, (iii) that it has an abuse liability similar to morphine and (iv) that prescribers and pharmacists should be cautious in prescribing or dispensing the drug where there is "an increased risk of misuse, abuse or diversion." These efforts, as the FDA stated on its internet website at the time of the revisions, were "intended to *change prescription practices* as well as increase the

[4] PPLP Minutes of FDA/PPLP Meeting, April 23, 2001.
[5] FDA Meeting Minutes of FDA/PPLP Meeting, April 23, 2001.

physicians' focus on the potential for abuse, misuse, and diversion . . . and *lessen the chance that OxyContin will be prescribed inappropriately* . . .." (emphasis added).[6]

On January 17, 2003, the FDA issued a Warning Letter to PPLP citing the company for disseminating misleading OxyContin advertisements in the October and November 2002 issues of the *Journal of the American Medical Association*. Among the FDA's stated reasons for its letter was PPLP's failure to present and disclose "critical" safety information in its OxyContin promotions. Following this Warning Letter, the Petitioner initiated an investigation into PPLP's marketing practices and requested that the company produce documents responsive to specific document requests. PPLP voluntarily complied with this request and cooperated with Petitioner's investigation, producing more than forty-thousand documents over a three month time period. In addition to reviewing documents produced by PPLP, the Petitioner also conducted interviews of former PPLP sales representatives, interviewed healthcare professionals and reviewed other publicly available information.

On September 8, 2003, the Petitioner met with senior PPLP executives to discuss concerns arising out of the investigation. Petitioner met again with PPLP executives on November 17, 2003. In conjunction with both of these meetings PPLP voluntarily provided the Petitioner with additional documents and information relevant to the issues discussed.[7]

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[6] FDA Talk Paper, July 25, 2001. PPLP appears to have a completely different interpretation of the purpose of the drug's 2001 revised indication. The FDA believed the old indication was "too broad" and the drug was "not appropriate for ambulatory and post-operative use...." PPLP Minutes of FDA/PPLP Meeting, April 23, 2001. As a result, the FDA and PPLP negotiated changes to the labeling in July 2001 which were intended to "change prescription practices." FDA Talk Paper, July 25, 2001. Although the FDA may have believed the revisions narrowed the indication, PPLP, in its 2002 OxyContin budget plan clearly felt the labeling changes "expanded the indication .... This broad labeling is likely to never again be available for an opioid seeking FDA approval. This may give OxyContin Tablets a competitive advantage." 2002 OxyContin Budget Plan. Further, PPLP reiterated in its plan that one of its primary "communication objectives" for 2002, was to "[b]roaden Oxycontin Tablets usage in the management of pain" and "stressed" one area to focus was "post-operative pain...." 2002 OxyContin Budget Plan.

[7] *See* discussion *infra*, Section V.

As will be discussed in the Statement of Factual Grounds, the Petitioner's investigation has determined that a relatively large percentage of prescriptions for OxyContin are being written off-label at dosing intervals not recommended in the manufacturer's guidelines or in the FDA approval, a practice which may adversely affect the health of certain patients who are prescribed the drug in this manner. In addition, Petitioner's investigation revealed that such off-label prescribing may not only affect patient health, but may also contribute to increased availability of the drug for illicit purposes.

Evidence developed through Petitioner's investigation revealed that many prescribers are prescribing the drug at dosing intervals that are shorter than the manufacturer's q12h recommended guideline, apparently unaware that in doing so, they may be placing their patients at risk of incurring increased incidence of side effects and possibly serious adverse reactions due to the pharmacologic action of this controlled-release drug when prescribed in this manner. For example, increasing a patient's total daily dose of oxycodone by prescribing an additional dose of OxyContin, once every eight hours ("q8h"), rather than increasing the q12h dose, will cause a more rapid accumulation of oxycodone, thereby possibly raising oxycodone plasma concentrations above the level deemed safe in clinical tests. This prescribing practice is not within the manufacturer's OxyContin dosing guidelines approved by the FDA. The evidence also demonstrates that the trend of prescribers writing OxyContin scripts for dosing intervals shorter than q12h has been increasing; and that PPLP has become quite concerned that prescribing in this manner could, and for certain at-risk patients - - probably did - - lead to increased patient side effects and adverse reactions, a consequence that is not explicitly stated in the drug's labeling. PPLP has also become concerned that increasing the number of OxyContin

doses beyond the recommended two daily doses increases the potential that the additional doses may be diverted for illicit use.

For the reasons that follow, Petitioner believes that practitioners and the public have not been fully informed of the potential risks associated with these practices. The purpose of this Petition, therefore, is to bring this evidence to the Commissioner and request that the FDA fully consider the information and, if deemed appropriate, take the action proposed below by the Petitioner or such other steps as are necessary to ensure that prescribers receive complete, adequate warnings of the health ramifications of this potentially problematic prescribing practice, so that they can factor the increased risks into their prescription decisions and provide more fully informed treatment to their patients who need effective and appropriate pain relief.[8]

II. ACTION REQUESTED

21 C.F.R. § 201.57 requires drug manufacturers to include certain information in their labeling, including warnings, precautions and the identification of adverse reactions associated with the use of the drug.[9] The Federal Food, Drug and Cosmetic Act provides that a drug shall be deemed to be "misbranded" if its labeling is "false or misleading in any particular." 21 U.S.C. § 352 (a). Pursuant to 21 C.F.R. § 201.57 and 21 U.S.C. § 352 (a), the Petitioner requests that the Commissioner act immediately to require PPLP to inform all prescribers of the potential risks associated with prescribing OxyContin at dosing intervals less than q12h. Such immediate action, as requested below, must include the dissemination of specific warning information to

[8] Full and clear disclosure of the potential for adverse reactions takes on even greater urgency following a recent court decision invalidating certain of PPLP's patents related to OxyContin due to inequitable conduct before the Patent and Trademark Office, leading to the potential for generic versions of the drug to be made available for sale in the near future. *See* n.2, *supra*.

[9] A prescription drug's "labeling" includes "all written, printed or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce." 21 C.F.R. § 1.3.

healthcare professionals related to appropriate prescribing of OxyContin and the revision of the current safety labeling of OxyContin, including:

A. Revising the Black Box Label

The following warning should be required to be added to the labeling of OxyContin:

> **WARNING:** (The following is in addition to the warnings currently contained in the labeling)
>
> **The recommended dosing guideline for OxyContin is q12h. The side effect profiles and other clinical documentation only support this dosing schedule. Increasing the patient's total daily oxycodone dose by adding one or more doses is not within the recommended dosing guidelines. Dosing OxyContin at intervals of q8h or shorter may cause an increase in oxycodone plasma concentrations and thereby increase the risks of side effects such as euphoria and sedation. Proper dosing further minimizes the potential for abuse and diversion.**

B. Strengthened Warning and Safety Labeling

Increasing the patient's total daily dose of oxycodone by prescribing OxyContin at intervals shorter than q12h will increase oxycodone concentration in the plasma to levels that may exceed the levels depicted in the OxyContin labeling (Plasma Oxycodone by Time).[10] Titrating the patient in this manner by increasing the dosing frequency to q8h or more frequently will cause acute successive increases in plasma concentrations of oxycodone and is not within the recommended dosing guidelines. The increased plasma concentrations will be most acute in the time period it takes for the patient to achieve steady-state.

Further, increasing the daily dose of oxycodone by increasing the dosing frequency will alter the side effect and adverse reaction profiles contained in the OxyContin package insert. Titrating the patient's total daily dose of oxycodone by shortening the interval between

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[10] *See infra* Table 2, Section III.C.2.

administration to less than q12h for the 80mg and 160mg doses of OxyContin further increases the already heightened risks attendant with prescribing these dosage strengths. This information should be added to relevant sections of the labeling, including but not limited to, the following sections: Warnings, Special Populations, Precautions, Adverse Reactions, Dosage and Administration – General Principles, Individualization of Dosage and Special Instructions for OxyContin 80mg and 160mg Tablets. In addition, adverse drug reactions associated with this dosing schedule identified and reported during post-approval use of OxyContin should be included in a Post-Marketing Experience section added to the drug's labeling.

C. The Issuance of a "Dear Healthcare Professional" Letter

PPLP should be required immediately to inform all prescribers of controlled substances in the United States about the potential risks of prescribing OxyContin at dosing intervals shorter than q12h.

D. FDA Notice to Healthcare Practitioners and the Public.

In addition, or as an alternative, to action by PPLP, the FDA should disseminate these warnings through a Safety Alert, Public Health Advisory, Talk Paper or Urgent Notice.

III. STATEMENT OF FACTUAL GROUNDS

A. The Pharmacokinetics of OxyContin and the Science of q12h

OxyContin is a controlled-release opioid that was designed to deliver a consistent level of oxycodone for 12 hours. The drug's patented delivery system - - the "AcroContin™" system[11] - - is constructed scientifically for q12h or biphasic absorption. Biphasic absorption describes a

[11] PPLP's internal documents stress that it is essential for prescribers to understand the difference between OxyContin's "AcroContin™ delivery system," which is intended for q12h administration, and MS-Contin's "Contin" delivery system, where the "duration of action is 8-12 hours." *OxyContin q12h Workshop*, (July 25, 2001) (hereinafter "*OxyContin q12h Workshop*").

two-stage process by which the oxycodone in the OxyContin tablet is dissolved and absorbed. The two stages comprise an initial rapid release stage, where oxycodone from the tablet's surface is absorbed and onset of analgesia occurs within 42 minutes to one hour, followed by a prolonged stage where the oxycodone is slowly diffused through the tablet's matrix and absorbed. According to PPLP, this means that within the first two hours of taking the drug, 38% of the available oxycodone in each tablet is absorbed into the bloodstream, with the remaining 62% delivered slowly over the next 10 hours.

OxyContin's labeling specifically provides that the elimination half-life of OxyContin - - the time it takes to decrease the plasma concentration of the oxycodone found in each tablet to half its value - - is 4.5 hours. The expected elimination half-life of a drug is a central component of the time it will take a patient to reach equilibrium, which is essentially the point at which the amount of the drug entering the body equals the amount being eliminated or excreted. This process is generally referred to as "steady-state." When the amount of a patient's total daily dose of a drug is increased, the concentration of that drug in the plasma will continually climb until steady state is reached, at which point the drug concentration level will again flatten out or plateau. Generally, it takes five half-lives to reach steady state; hence, the longer the elimination half-life of a drug, the longer it takes to reach steady-state and, accordingly, the greater the concentration of the drug in the plasma will increase before it plateaus.

Similarly, if the total daily dose of a drug is increased at the same time that the dosing interval is decreased, there will be even greater accumulation of the drug in the plasma because more drug is being absorbed and metabolized than is being excreted. This will result in higher drug concentrations in a compressed period of time. This process will continue until equilibrium or steady-state is again reached. If, however, drug concentrations exceed the therapeutic

threshold (the point at which maximum tolerated side effects occur), then the patient runs the risk of experiencing potentially significant adverse events.

The goal of any long-term drug administration regimen - - such as an OxyContin regimen - - is to achieve a steady state plateau that results in a relatively consistent and stable level of oxycodone concentration, and thus, pain relief. According to PPLP, clinical testing of OxyContin demonstrated that steady state levels were reached within 24-36 hours of the initiation of dosing.

The OxyContin package insert contains cautionary language in two primary areas that are particularly relevant to this Petition. First, prescribers are advised to be especially vigilant when prescribing the 80mg and 160mg doses to patients not previously exposed to opioids, as these strengths could cause fatal respiratory depression. Second, prescribers are advised that plasma concentrations of oxycodone may be even greater for patients in certain populations whose ability to eliminate the drug from their systems might be compromised to some degree. This is particularly relevant to the elderly (over 65 years), and patients with renal (kidney) or hepatic (liver) impairment who may, as a result, have higher oxycodone plasma concentrations than other patient populations. As long as initiation of therapy and dosing are "appropriate," however, the insert continues, no "untoward or unexpected side effects" were seen in these populations.[12]

There are 29 references in the current OxyContin package insert that support q12h dosing. All of the existing absorption data and blood level information contained therein is based on q12h dosing principles and side effect profiles, which indicate that "sedation" often does not persist beyond a few days and that the occurrence of "euphoria" was reported in less than 5% of patients participating in the clinical trials that supported the FDA's approval of

[12] OxyContin™ package insert. ©2001 Purdue Pharma L.P. Stamford, CT 06901.

OxyContin.[13] Equally important, PPLP's internal documents indicate that "100% of patients in clinical trials were dosed at q12h" and the package insert states "[t]here is no clinical information on dosing intervals shorter than q12h." In short, all of the PPLP recommended prescribing guidelines for OxyContin, safety information and the FDA approval for marketing are based on q12h dosing. As the Director of the FDA's Controlled Substance Staff stated when discussing the drug's 12 hour controlled-release formulation, "the safety of the drug is based on taking the drug exactly as intended."[14]

B. PPLP's Ability to Track OxyContin Prescriptions

Drug manufacturers use increasingly sophisticated data collection techniques and resources to track prescription generation. Through these sources, a company such as PPLP can determine which drugs are being dispensed from pharmacies in a given locale or even which drugs a specific physician prescribes. The data and other information gleaned from the prescriptions are then used by the manufacturer to formulate the marketing plan for its products. PPLP purchases several such data products from IMS Health.[15] One service, the "National Prescription Audit Plus," is a national sample of about 22,000 retail pharmacies, which tracks prescriptions from these pharmacies and extrapolates the data to the national level. This information allows PPLP to see specific data, including new and refill prescriptions filled by the pharmacy, prescriber specialty, number of tablets dispensed and length of therapy. A second

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[13] Euphoria is described as a unique sense of well being that addicts experience when using their drug of choice. Grinstead, S., A.D., M.A., A.C.R.P.S., *Understanding Addiction* (hereinafter "*Understanding Addiction*"). Available at: http://www.addiction-free.com/pain_management_&_addiction_understanding_addiction.htm. According to the OxyContin package insert, the risk of experiencing euphoria when taking OxyContin q12h is very low and the potential for developing addiction is "rare."

[14] Comments of Deborah Leiderman, M.D., FDA Consumer, September-October 2001 issue.

[15] Testimony of PPLP's Chief Executive Officer Michael Friedman. *Oxycontin: Its Use and Abuse.* Hearing before the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce. House of Representatives. August 28, 2001. IMS Health is a supplier of market research, business analysis, forecasting and sales management services to the global pharmaceutical industry.

service PPLP uses is the "Xponent" report, which provides PPLP with prescription information at the prescriber level. Through this service, PPLP receives data for individual prescribers on a monthly basis. The data includes new and refill prescriptions, total dollars per drug prescribed and the number of days of therapy. Using the two services, PPLP can determine, for example, which physicians are high prescribers of Percocet, a short-acting opioid, and then target the physician for a sales call to promote OxyContin. In addition to the aforementioned data services, IMS Health offers to at least two additional databases: the National Disease and Therapeutic Index ("NDTI") and National Prescription Audit ("NPA").

One specific piece of information PPLP received through its subscription to IMS Health databases was the dosing schedule data for OxyContin. The dosing schedule data is a statistical breakdown, by year, of OxyContin dosing schedules, *i.e.,* the percentage of prescriptions written for once a day administration, q12h, q8h, or even more frequently.[16] The data is further broken down so that PPLP can determine dosing schedules for specific strengths of OxyContin; for instance in a given year, PPLP knows the percentage of prescriptions written q12h for the 10mg, 20mg, 40mg, 80mg and 160mg strengths.

Combining all the data elements gives PPLP significant market intelligence that not only bears on its marketing efforts, but also identifies OxyContin prescribing trends that may help the company evaluate the nature, scope and locale of OxyContin abuse and diversion, as well as potential problematic prescribing practices by specific physicians and other prescribers.

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[16] The FDA, as part of the preliminary sharing of information surrounding the July, 2001 revisions to the drug's labeling, was particularly interested in the prescription and marketing data PPLP used for OxyContin, and requested such information from PPLP during teleconferences on April 20, 2001 and August 30, 2001. PPLP provided the FDA on May 16, 2001 and again on September 4, 2001 with information on the types of data services it used, but it does not appear, based on information the company produced to Petitioner pursuant to its investigation, that PPLP gave the FDA information on the OxyContin dosing schedules.

C. The "Problem": Dosing OxyContin More Frequently

Despite the fact that the OxyContin package insert both before and after the July, 2001 revisions only supports dosing at q12h, relevant data shows clearly that a significant number of prescribers are prescribing OxyContin at dosing intervals shorter than q12h. Based on PPLP's own internal documents, including IMS Health data, the company was aware as early as 1998 that 12.1% of all OxyContin prescriptions were written q8h or more frequently. This trend of prescribing outside the recommended dosing schedule continued to increase over succeeding years, moving to 14% in 2000, 20.2% in 2001, before dropping slightly to 18% in 2002. Equally important as the overall dosing data is the specific data related to individual tablet strengths, and in particular the three most powerful OxyContin dosage strengths. In the year 2000, 17.5% of the 40mg, 18.4% of the 160mg, and 23.8% of the 80mg strength - - almost one-quarter of all prescriptions at that strength - - were prescribed q8h or more frequently.

In a study reported in the *Journal of Managed Care Pharmacy* in 2003, researchers studied prescribing trends for OxyContin and the Duragesic patch.[17] Of the 437 OxyContin patients studied from six states (including Connecticut), the mean frequency of administrations per day was q8h, and the average time interval between administrations was 7.8 hours. Only 17.5% of the OxyContin patients surveyed had an average interval between administrations of 12 or more hours.[18] The study concluded that OxyContin "appears to be used in a manner inconsistent with the standard recommendation in [PPLP's package insert]."[19]

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[17] Ackerman, S., Mordin, M., et al., *Patient-Reported Utilization Patterns of Fentanyl Transdermal System and Oxycodone Hydrochloride Controlled-Release Among Patients With Nonmalignant Pain*, 9 Journal of Managed Care Pharmacy, May/June 2003 (hereinafter, "*Ackerman Study*"). This study was not part of PPLP's document production to Petitioner.

[18] These numbers may still underestimate the actual percentage of prescriptions dosed at q8h or more frequently. Another study reviewing OxyContin dosing frequencies in patients with chronic benign pain indicated that 86.8% of patients taking OxyContin were dosed q8h or more frequently. Adams, D., Bhakta, G., *et al.*, *Retrospective Assessment of Frequency of Dosing of Sustained Release Opiate Preparations in Chronic Pain Patients* (2002). The abstract of this study was produced to Petitioner by PPLP. Further, many OxyContin prescriptions are written for

Prescribing a drug in a manner that is inconsistent with the manufacturer's labeling is considered "off-label" prescribing. Although FDA regulations prohibit a manufacturer from marketing its drug for off-label uses, prescribers are not so constrained. In fact, physicians commonly prescribe drugs for uses not indicated in the drug's package insert. Concern arises if there is evidence that the off-label use presents a safety risk to the patient, especially if the manufacturer may have information of such possible adverse health consequences from off-label prescribing and fails to adequately warn the healthcare professional community of such risks.

Based on evidence in PPLP's internal documents, the company has been very concerned about physicians prescribing OxyContin q8h or more frequently. According to documents from a presentation developed in July 2001 and presented to PPLP's sales staff on several occasions since, the company informed its personnel that "Oxycontin is prescribed q8h or shorter 19.5% of the time."[20] This equates to "351,000 [OxyContin scripts] ... dosed at q8h" in the year 2001, meaning that "1 out of every 5 OxyContin scripts was outside [the package insert.]"[21] PPLP told its personnel that these numbers were "unacceptable,"[22] and, at its March 2002 National Sales Meeting, senior sales and marketing executives characterized this prescribing practice as a "problem."[23] Another internal document, written by a PPLP saleswoman to her staff, stated

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twice-a-day administration ("Bid") rather than q12h. Although q12h is essentially a Bid prescription, it is much more specific and the medication is intended to be taken at specific times. Bid, on the other hand, can be taken any time twice during the day. For example, Bid prescriptions may result in a patient taking the drug at breakfast and early afternoon, which is less than a full 12 hours between intervals. Alternatively, the patient may take the drug more than twelve hours apart, wherein the pain will return and the individual might think she needs a three doses per day to adequately control the pain.

[19] *See Ackerman Study, supra* footnote 17.

[20] *OxyContin q12h Workshop.*

[21] *Id.*

[22] *Id.*

[23] *Minimize Abuse/Diversion of Opioids*, PPLP National Sales Meeting, March, 2002 (herinafter, "*Minimize Abuse/ Diversion of Opioids*").

"there is no Q8 dosing with OxyContin. The action of adding a dose, as opposed to increasing the Q12h dose, needs to be nipped in the bud. NOW!!"[24]

Many of these off-label scripts were written by primary care physicians, a group which may not be as experienced in the proper prescribing of opioids as are orthopedic surgeons or oncologists.[25] One document taken from PPLP's presentation to its sales staff emphasized that 27.8% of OxyContin prescriptions written by family practice physicians and general practitioners were dosed at q8h or more frequently in 2001. The document stressed that "these numbers are very scary.... Look especially hard at the FP/GP [family practice/general practitioner] percentages - - they are the worst offenders, and therefore, require the most education on Oxy's dosing."[26] PPLP's documents expressly point out that practitioners are "accustomed to prescribing based on half-lives" which, given the drug's relatively short 4.5 hour elimination half-life, "explain[s] why clinicians will so readily go to Q8h dosing."[27] But basing dosing frequency decisions for OxyContin solely on the drug's half-life is a fallacy. Indeed, as the company pointed out to its sales representatives, "[c]linicians need to understand that with long-acting products, the delivery system determines the dosing, not the half-life."[28]

The drug's half-life is also used by physicians in determining when it is safe to increase a patient's total daily dose of oxycodone if the current dose fails to sufficiently relieve a patient's pain. Generally, clinicians believe it is safe to increase the dosage after steady-state is achieved, normally calculated at five half-lives. It is only after this point is reached that the therapeutic effects of the drug can be observed. Before that point, drug concentrations are continuing to

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[24] *Q12h vs. Q8h Warfare.* The document was used by PPLP's North Atlantic Region at least as early as August 2, 1999.

[25] *OxyContin q12h Workshop.* It is clear, from PPLP's 2003 OxyContin Marketing Plan, that much of the company's marketing efforts are directed at these primary care physicians. In 2002, primary care physicians accounted for 47% of all prescriptions written for OxyContin.

[26] *OxyContin q12h Workshop.*

[27] *Id.*

[28] *Id.*

increase, so the maximal response to drug use cannot be fully evaluated. Therefore, if a patient's dosage is increased again before new steady-state drug concentrations have been established - - perhaps out of the mistaken notion that the new dose is still not adequate to control the patient's pain - - then the steady-state concentrations will be much higher than they otherwise should have been to achieve appropriate pain relief. Elevated drug concentrations will greatly increase the potential for significant side effects and adverse events. OxyContin's labeling recommends that dosage adjustment may be carried out "every 1 to 2 days."

PPLP executives advised its personnel that a physician who prescribes off-label is not committing "malpractice, and we should never suggest that the physician should be held accountable for prescribing outside the package insert . . ." ; rather, "[w]e shouldn't 'beat up' doctors who are treating pain with a dose of q8h, we should . . . refocus them back to q12h."[29] One former PPLP sales representative interviewed as part of the Petitioner's investigation confirmed the company was very concerned about the q8h problem and stated the company "drilled" it into its detailers that they should urge physicians, if the sales representative learned a physician was prescribing outside the recommended dosing guidelines, not to prescribe the drug more frequently than q12h.[30]

According to the sales representative, the company's concern was twofold: first, there was some evidence of undesirable side effects associated with long-term administration at increased dosing frequencies; second, PPLP feared that managed care organizations and third-party payers would eventually place additional administrative requirements and restrictions on

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[29] *OxyContin q12h Workshop*. Although PPLP advised its sales personnel that off-label prescribing is not "malpractice," there may be a claim of malpractice if the patient suffers harm as a result. *See Sita v. Danek Medical, Inc.*, 43 F. Supp.2d 245, 263 (E.D.N.Y. 1999) (noting that "[a] doctor using an FDA-approved drug ... for an off-label use bears the risk of being sued for malpractice if the plaintiff is harmed by an unwarranted use of the drug.")

[30] The salesman's description of PPLP's concern over this practice is reflected in several written admonishments to PPLP sales personnel to try and stem the practice. One such document, entitled *Q12H versus Q8H*, was written by PPLP's South Western Region Regional Manager in January, 2000 (hereinafter "*Q12H versus Q8H*").

physicians prescribing OxyContin q8h or more frequently, primarily because there were cheaper alternatives that were just as effective at q8h and that were specifically approved and recommended for q8h dosing, like MS-Contin (a PPLP drug) and generic controlled-release morphine-sulfate. Additional administrative requirements by third-party payers and managed care organizations, such as placing a drug on what is commonly referred to as "prior authorization," will often negatively impact sales of the drug. Both of these concerns are corroborated in PPLP's internal documents.

1. The Nature of the Problem

The evidence provided to Petitioner suggests PPLP was concerned about the practice of prescribing OxyContin at intervals shorter than q12h because shorter intervals could increase oxycodone blood levels above the level deemed safe through clinical testing when the extra dose is accompanied by an increase in the patient's total daily oxycodone dose. In other words, as discussed above, the drug is intended to work over a 12 hour period. When a physician prescribes at q8h a drug that is designed to release oxycodone over a 12 hour period, there is an overlapping period of time when two doses of OxyContin are affecting the patient at once. For example, given the biphasic absorption process, a patient taking OxyContin at 8 a.m. will have an initial absorption of 38% of the oxycodone within the first two hours of taking the drug. According to OxyContin's recommended dosing guideline of q12h, the next dose should not be administered until 8 p.m. Under the q12h dosing regimen, the remaining 62% of the oxycodone is absorbed, distributed, metabolized and excreted during the prolonged phase, hours 3-12 (10 a.m. – 8 p.m.).

But when a prescriber prescribes OxyContin q8h, the second dose will be administered at 4 p.m., which results in an overlap of doses with both doses working in the patient between the

hours of 4 p.m. to 8 p.m. (hours 9-12): the remaining dose of oxycodone from dose one (administered at 8 a.m.) and the initial absorption of oxycodone from dose two (administered at 4 p.m.). If the second dose is given early enough that not all of the first dose is eliminated, then the drug will start to accumulate and the patient will have higher concentrations of the drug in the plasma with the succeeding doses. Thus, in the condensed time span when both doses are working at the same time, this dosing schedule "will increase blood levels"[31] and such dosing *is "not within the recommended dosing guidelines."* (emphasis in the original).[32]

For the majority of patients, these drug plasma concentrations will continue to accumulate until the patient reaches steady-state. During the time period between dose and dosing interval adjustment, and the time to reach steady-state, patients are potentially exposed to additional risk from successively increased concentrations of oxycodone occurring at shorter intervals. While PPLP's OxyContin labeling maintains that steady-state is reached in 24-36 hours - - based on a stated elimination half-life of 4.5 hours, the company's executives conceded in a meeting with Petitioner on November 17, 2003 that the true elimination half-life for OxyContin is closer to 10 hours.[33] This means that the time to reach steady-state may be longer than 24-36 hours, and perhaps as long as 48-50 hours. If such is the case, then oxycodone plasma concentration will not plateau at 24-36 hours, but will continue to build for a longer period of time. If this is truly the case, it may be inappropriate to make dosage adjustment decisions after only 1 day, as the drug's labeling suggests is appropriate, since steady-state may not be reached for closer to 50 hours. As stated above, if the dosage is adjusted before steady-state is reached from the previous dosage adjustment, the accumulation effect is compounded and the result will be even higher drug concentrations in the plasma.

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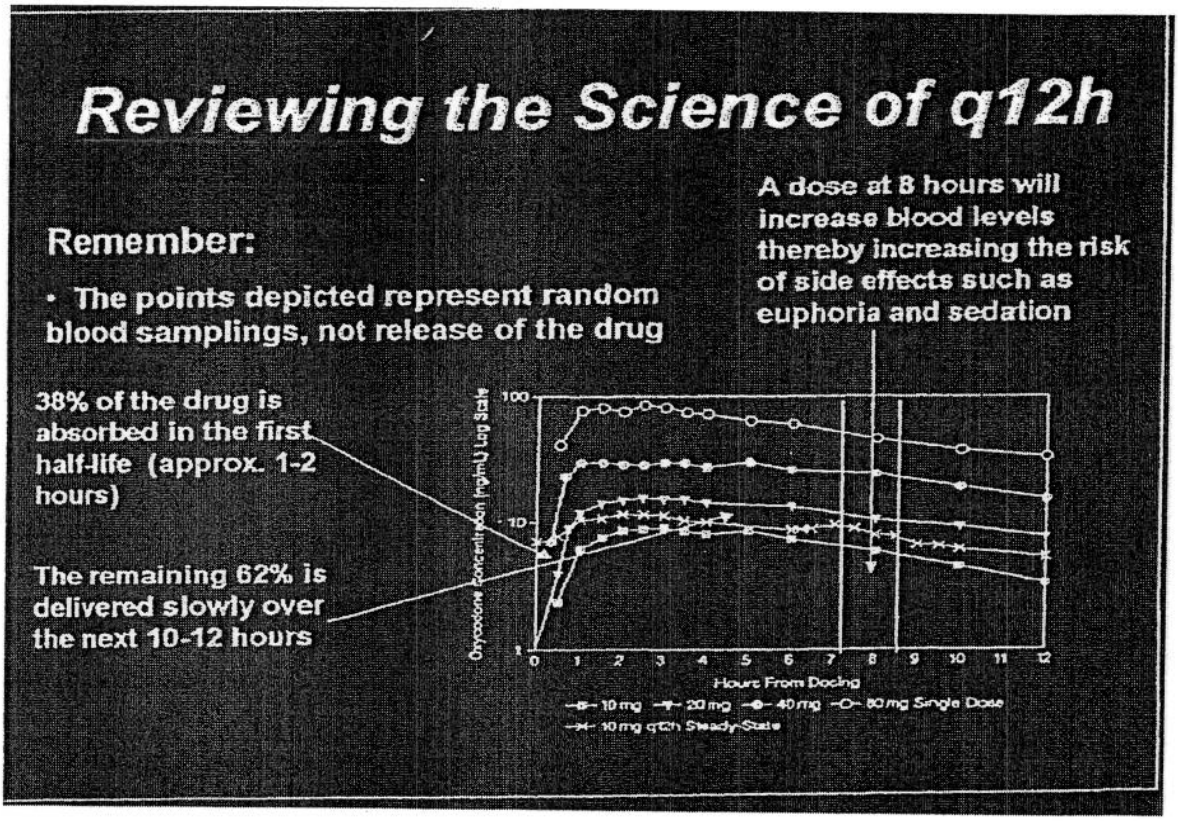
[31] *OxyContin q12h Workshop.*
[32] *Minimize Abuse/Diversion of Oxycontin.*
[33] *See* discussion *infra*, Section V.

Dosing frequencies shorter than the recommended dosing guidelines may, therefore, increase the risks of side effects in patients taking OxyContin. During its presentations to its sales staff, PPLP trainers showed a graph depicting the oxycodone plasma concentration curve for the OxyContin 10mg, 20mg, 40mg and 80mg dosages. The graph is similar to the one used in the current OxyContin package insert except that this graph had two vertical lines bracketing the blood sampling for each dosage at hour eight, and an arrow drawn to this area to highlight the point that "[a] dose at 8 hours *will increase the blood levels thereby increasing the risk of side effects such as euphoria and sedation.*"[34] (emphasis added). (*See* Table 1 below, Reviewing the Science of q12h).

TABLE 1



[34] *OxyContin q12h Workshop*. If people experience euphoria when using a drug, "they are in high risk of getting addicted to the drug." *See, supra* footnote 13, *Understanding Addiction.* "People become addicted to this state of euphoria." *Id.* Moreover, the stronger the positive reinforcement (euphoria) that is experienced when they use their drug of choice, the greater the risk that they will become addicted. *Id.*

Another internal document sent to PPLP sales personnel working in the South Western Region cautioned "if a patient is dosed Q8H, then patients are more likely to get more side effects due to overlapping blood levels."[35] In short, PPLP's experts and senior sales executives concluded that q8h dosing increases oxycodone plasma concentration which increases "the risk of side effects." Prescribing even more frequent dosing regimens, such as every 6 hours or every 4 hours, in combination with an increase in the total daily dose of oxycodone, may exacerbate the potential problem. Internal PPLP documents state that in 2001, 6% of the OxyContin prescriptions written that year were dosed q6h or q4h, and in the year 2000, 6% of the 80mg strength tablets were dosed more frequently than q8h.

The risk of a potential increase in side effects from higher dosing is even more pronounced for certain patient populations. For example, the OxyContin labeling warns that plasma concentrations of oxycodone are approximately 15% greater in geriatric patients due to a slight reduction in their ability to eliminate the oxycodone from their systems. Likewise, patients with renal or liver disease often have a decreased ability to adequately eliminate certain drugs, including oxycodone, from their systems. If the elimination process is slowed, and the patient takes the drug more frequently than q12h, additional drug accumulation may occur over a longer time period than occurs in the average patient population because the slowed elimination process in these patients will likely result in a longer time to reach steady-state. This could result in potentially toxic concentrations being reached, rendering patients even more susceptible to side effects and more serious adverse events if their already slightly elevated plasma concentrations continue to increase with each dose.

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[35] *Q12H versus Q8H.*

2. Expert Medical Opinion Supporting the Petition

As support for its Petition, the Petitioner consulted one clinician and one medicinal chemist with experience and expertise particular to the field of medicine, pharmacology and medicinal chemistry.

Alexandros Makriyannis, Ph.D., is a medicinal chemist and professor at the University of Connecticut School of Pharmacy and the Director of that institution's Center for Drug Discovery (*See* Exhibit 1, *Curriculum Vitae*). Dr. Makriyannis confirmed that taking the same individual doses of OxyContin q8h instead of q12h would result in a significant increase of the oxycodone concentration at hours nine and ten of the first dose. Dr. Makriyannis explained that this increase in plasma concentration of oxycodone is due to the additive effect of the two consequent doses of OxyContin. As Dr. Makriyannis described it, at that point of convergence (hours nine and ten) there is still a significant amount of oxycodone from the first dose being absorbed into the bloodstream as part of the prolonged (dissolution/diffusion) phase of OxyContin's delivery system. Then, at that same time, there is the introduction into the bloodstream of an additional, larger amount of oxycodone resulting from the initial phase of absorption of the second dose when taken, for example, q8h. According to Dr. Makriyannis, the intersection of these two doses of oxycodone at hours nine and ten increases the expected "initial burst" of the OxyContin dose.[36] Prescribing the same single doses at intervals shorter than q12h may result in peak plasma concentrations of oxycodone "leveling off at higher plasma concentrations." Dr. Makriyannis believes that prolonged prescribing in this manner could lead to increased steady-state levels of the drug with the risk of undesirable side effects. (*See* Table 2 below, the Plasma Oxycodone by Time Graph from the current OxyContin Package Insert.)

[36] One former PPLP salesman interviewed described this dyanamic as a "bolus" or big dose of oxycodone.

It is Dr. Makriyannis' opinion that physicians may be prescribing outside the manufacturer's recommended guidelines to compensate for "end-of-dose failure," the inadequate pain relief some patients may experience during hours nine through twelve when taking OxyContin q12h. Dr. Makriyannis is "sympathetic" to physicians using this "off-label prescribing" methodology and did not see too much risk at the lower OxyContin strengths. However, according to Dr. Makriyannis, increasing the patient's total daily dose of oxycodone by prescribing the drug at intervals shorter than q8h, especially for the higher OxyContin strengths, may lead to high concentrations of oxycodone with potentially undesirable side effects.

Finally, Dr. Makriyannis' stated that addiction is often related to several factors, including: (i) the patient's genetic predisposition, (ii) the dosage, (iii) the time to onset of drug effect;[37] and (iv) the frequency of administration. Thus, an increase in the total daily dose of oxycodone due to the accelerated frequency of administration could increase the probability for addiction.[38] Dr. Makriyannis would "fully support" more information in the OxyContin package insert that discloses the potential consequences of prescribing high doses of the drug in dosing intervals less than q12h.

James O'Brien, Ph.D., M.D., is a toxicologist at the University of Connecticut Poison Control Center and was an Associate Professor at that institution's medical school for over 17 years with appointments in medicine, surgery, psychiatry and toxicology. As explained in more detail in the attached affidavit (*See* Exhibit 2), Dr. O'Brien discussed the effect q8h dosing would have on a patient's plasma concentration of oxycodone. According to Dr. O'Brien, if the

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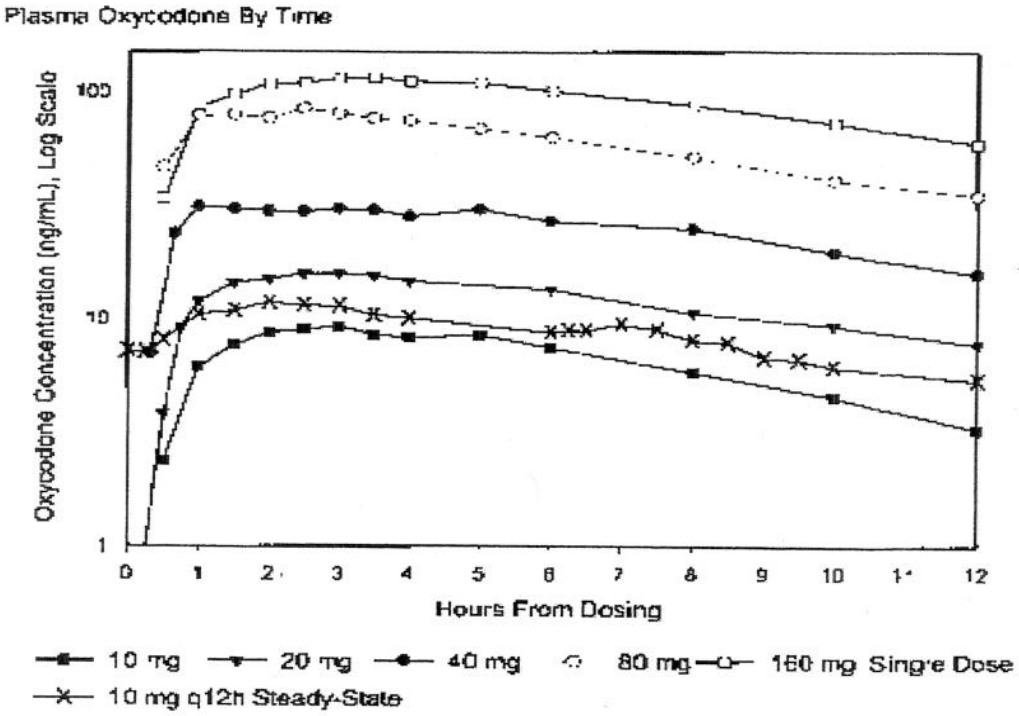
[37] Although difficult to quantify, the time to onset of peak plasma concentration of oxycodone may be somewhat accelerated due to the pharmacokinetics associated with prescribing OxyContin q8h or more frequently.

[38] Dr. James Zackney, of the University of Chicago stated that "euphoria appears to be a factor in opioid abuse...." *Research Eases Concerns About Use of Opioids to Relieve Pain*, Vol. 15, No. 1, N.I.D.A. Notes (March, 2000).

amount of oxycodone in the bloodstream is measured at different points in time over 12 hours, and these points are plotted on a graph, the curve for a controlled-release drug should be, over time, relatively flat, with slightly higher levels at hour 8 and a tail off at hour 12, when the next dose is supposed to be administered.

Table 2 below, the Plasma Oxycodone by Time Graph, from the current OxyContin package insert illustrates the plasma concentration of oxycodone prescribed at the recommended q12h:

TABLE 2



If, however, the prescriber increases the patient's total daily dose of oxycodone and shortens the dosing interval to q8h, the patient will receive the second dose at hour 8 rather than at hour 12. With OxyContin's unique AcroContin delivery system, this will cause one-third of

the second available dose of oxycodone to be absorbed within 1-2 hours of administration, with more of the drug entering the blood stream at a time when the plasma concentrations from the first dose of OxyContin are already higher than they would be at hour 12. That additional one-third dose of oxycodone will be "superimposed" on the dose of oxycodone still remaining in a patient's system from the prior dose's prolonged absorption phase, the period of time when the remaining two-thirds of oxycodone is slowly diffused and absorbed. This "super-imposing" process will cause "an increased accumulation of oxycodone and its less active metabolites in the plasma," leading to a build-up in the plasma concentration of oxycodone before steady-state is reached. As Dr. O'Brien explains it, if these oxycodone plasma concentrations were graphed over the first several days after dosage and dosing frequency adjustment, it would result in a "stepwise progression in the patient's plasma levels" - - a step ladder effect - - "due to a greater accumulation of the drug in a relatively short time."[39] Dr. O'Brien's opinion is that prescribing OxyContin q8h or more frequently is of special concern at OxyContin's higher dosages.

Dr. O'Brien states that such a prescribing pattern "will significantly raise the potential for a patient to incur an increase in the frequency and severity of side effects and, possibly, adverse events," particularly within "the first few days after dosage adjustment." This concern is intensified for those patients "whose ability to eliminate the drug is compromised," due to age, gender or disease. Longer time to eliminate the drug will result in a more rapid accumulation of oxycodone "from the increased dosing frequency, leading to a heightened potential for toxic concentrations. . . . making [these patients] more susceptible to increased occurrence of side effects or adverse events such as . . . hypoxia , and/or respiratory arrest." These are the chief

[39] Consistent with OxyContin's approved indication, many patients prescribed OxyContin will take it long-term. The FDA approved indication for OxyContin is for patients who need the "medication around the clock for an extended period of time." Thus, unlike, for example, a patient prescribed a short-term antibiotic to treat an infection, by definition many patients prescribed OxyContin will be taking it for months if not years.

concerns in opioid use and the most common cause in an overdose death. Additionally, it is Dr. O'Brien's opinion that because of the drug's biphasic delivery system, prescribing OxyContin q8h or more frequently "will raise the liklihood of increased euphoria which will add to the specter of the potential for abuse and psychological dependence to the drug."

3. Petitioner's Interviews with Patients or Patients' Family Members

Over the past two years Petitioner has conducted interviews with former OxyContin patients or family members of such patients. Of those interviewed who were prescribed OxyContin, each described serious side effects which they believed were caused by the drug. Similarly, family members of patients who died during the course of their treatment with OxyContin also related their strong belief that OxyContin was a precipitating factor in the death.

In August, 2001, Petitioner interviewed John Doe,[40] whose wife had passed away in June, 2001. Doe related that his wife suffered from Lyme disease and Graves' disease and was taking several medications to treat these conditions, including OxyContin. According to Doe, his wife, who was a registered nurse, had been prescribed OxyContin for over one year, beginning with an initial prescription of 10mg q8h which was eventually increased to 80mg q8h. During that time period, Doe's wife exhibited several disturbing side effects which Doe believed were related to the medication she was prescribed for her disease and to treat her pain. Among the side effects, Doe's wife complained of dizziness, disorientation and chest pain and, he added, he noticed she "gurgled while she slept." Doe stated that these side effects were "more pronounced" after the OxyContin dosage was increased to 80mg.

[40] The interviewee's name is not being used due to privacy concerns.

On the night before her death, Doe stated that his wife went to the emergency room because she was experiencing severe dizziness and chest pains. At the hospital she was examined by medical staff and released. She died early the following morning. Throughout the course of her treatment, and up until the time of her death, Doe's wife was under the care of both her primary care physician and a physiatrist. Doe strongly believed that his wife's death was a result of her use of OxyContin.

Petitioner has reviewed the medical examiner's report and the accompanying toxicology report for Doe's wife. In addition, Petitioner conducted a telephone interview with the medical examiner on August 14, 2001. The report determined the cause of death as "Oxycodone intoxication," and the manner of death as "Accident." The medical examiner stated that the toxicology report identified oxycodone blood levels of 1.1mg/L, and based on Doe's statement that his wife was prescribed OxyContin, the medical examiner concluded that she died as a result of an OxyContin overdose.

In addition to the incident described above, Petitioner's review of FDA postmarketing surveillance program ("MEDWATCH") adverse event reports submitted to the agency from 1999 through early 2003 (*see* discussion in Section III.D, below), where OxyContin was a named suspect medication, identified 49 adverse event reports where death was the outcome. **All of these reports indicate the decedent was prescribed OxyContin at least q8h or more frequently**. Petitioner's review of these 49 reports revealed 12 deaths where OxyContin may be considered a suspect cause. (*See* Appendix A attached hereto).

The following are excerpts from certain of these Reports:

- MEDWATCH report 200146 – A 55 year old female with a history of arthritis, depression and hypertension died on February 21, 2000. On February 15, 2000 the patient began taking OxyContin 10mg q12h, Elavil and Toprol XL. On February 16, 2000 the frequency and total dosage of the patient's OxyContin was

increased and the new prescription was 10mg q8h. On February 18, 2000 the OxyContin prescription was adjusted to 20mg q8h. On February 20, 2000 the OxyContin prescription was increased to 30mg q8h. On February 21, 2000 the patient died. The reporting pharmacist believes the death may be a result of a drug interaction.

- MEDWATCH report 200196 – A male of undetermined age died on an unspecified date of respiratory depression while taking OxyContin for AIDs, lymphoma, brain tumor and cancer. The patient was started on OxyContin 40mg q12h. When the pain increased, the patient's dose was adjusted to 80mg q8h. Thereafter, the dose was again increased to 80mg q6h "and that is when there was a code blue."

- MEDWATCH report 2010668 – A 41 year old female with a history of chronic low back pain was prescribed OxyContin 80mg q8h on April 22, 1998. On May 9, 1998, 18 days after the initiation of therapy, the patient died from a cerebrovascular accident. The prescribing physician determined the event "was possibly related to OxyContin therapy."

- MEDWATCH report 2013754 – A 50 year old female was prescribed OxyContin 20mg BID on July 27, 2001 for post-operative pain. In addition to the BID prescription, the patient was prescribed OxyContin q6h prn for breakthrough pain. On the morning of July 30, 2001, the patient's husband called the emergency medical service because the patient was unresponsive. The patient awoke shortly thereafter and refused to go to the hospital. The patient's husband convinced the patient to go to the hospital, however, in route, the patient again became unresponsive and was pronounced dead on arrival.

Besides being a potential suspect cause in patient deaths, OxyContin is the suspect cause of other serious medical problems in patients prescribed the drug. Petitioner interviewed Chelly Griffith, a 37 year old married mother with two children who lives in Davenport, Iowa. Ms. Griffith agreed to have her name used in this Petition. In January 1999, while caring for her daughter, Ms. Griffith aggravated a back injury she first sustained in 1995. After discussing treatment options with her physician and ruling out surgery, she was given a prescription for OxyContin 20mg q12h. Within days of beginning this treatment regimen, Ms. Griffith experienced dizziness, tiredness and constipation and although she continued to take the

medication, she complained to her physician that the OxyContin did not effectively control her pain.

Because the medication was inadequately controlling her pain, her physician recommended increasing her total daily dose of oxycodone from 40mg to 60mg by increasing the frequency of administration of her 20mg dose from q12h to q8h (for a total of 60mg daily). Ms. Griffith recalls that she discussed the increase in dosing frequency with her physician at the time and he assured her that it "was not a problem" and was consistent with OxyContin prescriptions he wrote for other patients when they informed him that the pain relief "didn't last for twelve hours." Although she continued to take the drug as prescribed, Ms.Griffith voiced concerns to her physician and the nurse practitioner, who briefly assumed a primary role in her treatment, that she suffered uncomfortable and, at times, immobilizing side effects which she believed were caused by OxyContin. Among these side effects were significant weight loss, dizziness, severe itching, nausea, abdominal pain, and a "floaty" or "buzz-like" feeling within the first one to two hours of taking each dose. Overriding her trepidation over all of these side effects, however, was Ms. Griffith's awareness that she was slowly "deteriorating" and losing control of her life: she still suffered from back pain, she was constantly depressed, and she developed an intense uncontrollable craving for the drug such that she "couldn't wait to get OxyContin in my body after I woke up each morning." Moreover, each dose of OxyContin only temporarily lessened her craving for the drug which ultimately recurred again "within a few hours" of each dose.

By the summer of 2000, Ms. Griffith's physician once more increased her OxyContin prescription in another effort to treat her inadequate pain control, this time increasing the dosage to 40mg q8h. According to Ms. Griffith, the new prescription only further intensified the side effects she already encountered from the drug which, by the summer of 2001, included numbness

throughout her body, double-vision, loss of smell and taste, tinnitus, decreased libido and urine retention. By this time she had also spent the better part of two years trying, unsuccessfully, to seek out medical assistance to help her overcome her self-described "addiction" to OxyContin.

In May 2002, acting on the advice of her orthopedic surgeon, Ms. Griffith attempted to wean herself from the drug. This attempt was short-lived, and ultimately unsuccessful, and she resumed taking the drug after only a brief respite. By September of that year, however, the side effects continued to escalate along with their severity. She began to develop uncontrollable tremors, countless body sores and the loss of her body hair. As a result of all these maladies she voluntarily admitted herself into a drug treatment facility in Illinois where she spent two and one-half days before leaving the program. Finally, later that month and with the help of her parents, Ms. Griffith spent one week going "cold turkey" in the basement of her parents' home before she was at last successful in her effort to stop taking the medication. Although she stated that she continues to experience pain everyday, Ms. Griffith only uses aspirin now to treat her discomfort. She still experiences tremors and bouts of memory loss but stated that most of the other side effects have abated and her eye sight has improved to the point where "I can again see the edges that surround a stop sign."

Petitioner has reviewed MEDWATCH adverse event reports submitted to the FDA (*see* discussion in Section III.D, below) where OxyContin was a named suspect medication in serious adverse events encountered by patients prescribed the drug. Petitioner has identified 247 adverse event reports submitted to the FDA from 1999 through early 2003 where the patient was prescribed OxyContin at least q8h or more frequently. These reports revealed 52 non-fatal serious adverse events where OxyContin may be considered a suspect cause of the event and which resulted in a life-threatening event, hospitalization, or some other medically significant

outcome. (*See* Appendix B attached hereto). Many of these adverse event reports describe side effects similar to those Ms. Griffith recounted during her interview, including drug dependence or withdrawal symptoms (12 reports), dizziness, myoclonic jerks, hair loss, nausea, somnolence and depression. These reports depict how the side effects often developed shortly after a patient's OxyContin dosing schedule was increased to q8h or more frequently, and subsided or disappeared altogether when the dose was reduced or the time interval between administration was increased.

The following are excerpts from certain of these Reports:

- MEDWATCH report USA-2002-0001088 – On an unspecified date, a 68 year old female was prescribed OxyContin 20mg q12h. The patient experienced ineffective pain relief and her dose was increased to 20mg q8h on an unspecified date. Following the increase in her prescription, the patient became sedated and dehydrated and required hospitalization. The OxyContin was discontinued thereafter

- MEDWATCH report USA-2002-0001811 – In November 2000 a 40 year old male was prescribed OxyContin 40mg q12h for pain related to an earlier automobile accident. Shortly thereafter, the prescription was increased to 40mg q8h. Approximately two months after the prescription was increased, the patient experienced convulsions lasting 2 to 18 minutes in length, bilateral leg numbness and urinary incontinence. The symptoms ceased approximately three weeks after OxyContin therapy was discontinued.

- MEDWATCH report 200906 – In March 2000 a 48 year old male was prescribed OxyContin 40mg q6h to q8h. In June 2000 the patient began experiencing panic attacks and claustrophobia approximately 45 minutes after taking a dose of OxyContin.

- MEDWATCH report USA-2002-0001378 – On July 10, 2000, a male of undetermined age was prescribed OxyContin 10mg q12h seven months after back surgery to repair ruptured disks. On August 7, 2000 the daily dose was increased to 10mg q8h. Approximately eight months later, the patient experienced continued somnolence, depression, amnesia, nausea, pruritis and drug addiction. The patient eventually received out-patient treatment for addiction and received methadone for symptoms of withdrawal.

- MEDWATCH report USA-2002-0002117 – A 41 year old female was prescribed OxyContin beginning in February 1998 for chronic back pain. The treatment

continued until March 20, 2001. The patient's initial prescription was OxyContin 20mg q8h. On unspecified dates her daily dose was increased to 40mg q8h and then 80mg q8h. The patient was hospitalized from March 20-26, 2001 to treat symptoms of addiction and received follow-up care for withdrawal symptoms.

D. Petitioner's Review of Reports Submitted to the FDA Medical Products Reporting Program

The FDA's regulations mandate that manufacturers of approved pharmaceuticals report all adverse events of which they are aware to the FDA and to provide as complete information as possible concerning the circumstances surrounding the report.[41] The information is organized and evaluated as part of the FDA's MEDWATCH program. The MEDWATCH program also relies heavily on health professionals (physicians, pharmacists, nurses, dentists and others) to voluntarily report serious adverse events they may observe in the course of their everyday clinical work. An adverse event report submitted to MEDWATCH may be a "spontaneous report" (a clinical observation originating outside of a formal study) or one based upon information a manufacturer may receive or develop via scientific literature or postmarketing studies. The FDA's position is that an adverse event ("AE") should be submitted to MEDWATCH whenever a serious adverse event *may* have been caused by that manufacturer's drug. Causality is not a prerequisite for reporting; suspicion that a medical product may be related to a serious event is sufficient reason for a report. Health professionals are encouraged, and manufacturers are required, to make these reports as soon as they become aware of the AE.

Petitioner has reviewed and analyzed MEDWATCH reports for OxyContin or oxycodone hydrochloride (controlled-release) submitted to the FDA by PPLP and/or health professionals covering the time period 1999 through early 2003. These reports were voluntarily produced to Petitioner by PPLP pursuant to Petitioner's investigation. The Petitioner's review and analysis was initiated to quantify, to the extent practicable given the limitations of the reports

[41] 21 C.F.R. § 314.80.

themselves,[42] the number of AE reports submitted for patients with a prescription for OxyContin q8h or more frequently, and to compare this information with the information contained in PPLP's documents pertaining to the percentage of OxyContin prescriptions written q8h or more frequently. Based on that data, Petitioner sought to determine whether it was more likely than not that there was a correlation between a prescription written q8h and an AE.

PPLP's internal documents indicate that in the year 1999, about 1 out of every 8 OxyContin prescriptions, or about 12%, were prescribed q8h or more frequently. In the year 2000, approximately 14% or 1 out of every 7 OxyContin prescriptions were prescribed q8h or more frequently. In the year 2001, 20.2% or 1 out of every 5 prescriptions were prescribed q8h or more frequently. And, in the year 2002, 18% of prescriptions were prescribed q8h or more frequently. Of the 2,880 AE reports reviewed and analyzed, Petitioner concludes 1,106 were most likely related to a patient prescribed OxyContin.[43] Of the universe of the 1,106 AE reports related to OxyContin patients, Petitioner identified 795 reports where the prescription, including dosing frequency, were specifically mentioned in the report. Of those cases, patients were prescribed OxyContin q8h or more frequently in 247 or 31% of the AEs reported.[44]

Petitioner's concerns over this prescribing practice are best illustrated by discussing the results of its AE analysis by year. In 1999, PPLP's data states 12.1% of OxyContin prescriptions

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[42] Because the identification of the patient and the health professional who made the report were redacted by PPLP prior to Petitioner receiving the report, it was difficult for the Petitioner to determine if a report was submitted to the FDA more than once. Nevertheless, despite these limitations, the review and analysis yielded important evidence supporting Petitioner's contention that OxyContin prescribed q8h or more frequently may increase the potential for side effects and adverse reactions. This contention is strengthened considering the FDA's acknowledgement that AE reporting is inherently underreported. It has been estimated that the MEDWATCH program receives less than 1% of suspected serious AE reports. If true, this means that those OxyContin cases identified and reviewed by Petitioner would "represent only a small portion of the number that have actually occurred." *The Clinical Impact of Adverse Event Reporting*, Center for Drug Evaluation and Research, FDA (October, 1996).

[43] The universe of 2,880 reports include AEs encountered by individuals who received the drug through apparently illicit sources and were, thus, not using the drug through a prescriber's prescription. These AE reports, once identified, were excluded from the analysis.

[44] 44 of the MEDWATCH reports included a mention that the AE was a "No Drug Effect." This appears to corroborate one of the findings in the *Ackerman Study*, *infra* footnote 17, which noted that 84.7% of patients surveyed indicated the duration of adequate pain relief was less than 8 hours. *Id.* at p. 227.

were written q8h or more frequently. In Petitioner's AE analysis for that year, 35% of AE reports contained a prescription for OxyContin q8h or more frequently, which is a much larger percentage of AEs than one would expect to encounter based on the percentage of prescriptions written for that dosing frequency. If the frequency of administration played no role in the generation of an AE report, Petitioner would have been expected to find that roughly 12% of the AE reports in 1999 were prescribed q8h or more frequently, the same percentage of OxyContin prescriptions written q8h or more frequently. A finding that 35% of the AE reports included a prescription q8h or more frequently is three times greater than one would expect if one had picked a report at random to see if it included such a prescription.

In 2000, PPLP's internal data indicates that 14%, or 1 out of every 7 OxyContin prescriptions, were q8h or more frequently, yet 22%, or nearly 1 out of every 4 AE reports, contained a prescription for OxyContin q8h or more frequently.[45] In 2001, PPLP's internal data indicates 20.2%, or 1 out of every 5 prescriptions, were for q8h or more frequently, yet Petitioner's AE analysis reveals that 37% of AEs, or more than 1 out of every 3 AEs reported to MEDWATCH, contained a prescription for OxyContin q8h or more frequently.[46] In 2002, 18% of prescriptions were written q8h or more frequently, whereas 36% of AE reports included these dosing frequencies.[47] Significantly, 109 of the 247 OxyContin AEs (44%) reported with a prescription of q8h or more frequently were for the 80mg or 160mg strengths of OxyContin. This finding - - that 44% of the AEs involved patients with a prescription strength of 80mg or more - - gives added credence to the concerns raised by Dr. O'Brien and Dr. Makriyannis that

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[45] A finding that 22% of the AE reports included a prescription q8h or more frequently is 57% more often than one would expect if one had picked a report at random to see if it included such a prescription.
[46] A finding that 37% of the AE reports in 2001 included a prescription q8h or more frequently is 88% more often than one would expect if one had picked a report at random to see if it included a such a prescription.
[47] A finding that 36% of the AE reports in 2002 included a prescription q8h or more frequently is 100% more often than one would expect if one had picked a report at random to see if it included such a prescription.

dosing these strengths at intervals shorter than q12h could raise the potential for an adverse outcome.

These statistical findings clearly indicate there is a much greater percentage of OxyContin AEs reported to MEDWATCH with a prescription for q8h or more frequently than would be expected based on the overall percentage of prescriptions written in that manner. Stated differently, if the dosing frequency played no factor in the potential for a patient incurring a subsequent AE, then the number of AE reports with q8h or more frequent prescriptions should basically mirror the overall percentage of prescriptions written in that manner. Given the significant percentage differential between the number of OxyContin prescriptions written q8h or more frequently, and the percentage of AE reports that have such prescriptions, the Petitioner believes that a sufficient basis exists from which the Commissioner may conclude that there is a correlation between increasing the dosing frequency of OxyContin prescriptions and the potential for an AE.

In a report issued in the summer of 2001, the Los Angeles County Department of Coroner studied the cases of 58 deaths where oxycodone was detected during the postmortem evaluation. The study covered the time frame 1996 to 2001. Of the 58 cases where oxycodone was detected, 27 were determined to be the controlled-release form of the drug, and each of these individuals had a prescription for OxyContin. Among the findings of the study was the fact that in 14 of the 27 cases, a number of intact tablets were found in the stomach, leading the authors of the study to question whether the cause of death was suicide or due to some other reason, such as the individual's misunderstanding of the proper administration of the painkiller. Of particular relevance to this Petition, however, and specific to the issue of whether there is a correlation between an OxyContin prescription written q8h or more frequently and a subsequent AE, is an

observation the authors include at the conclusion of their study: *"[a]nother interesting fact noted while evaluating the case histories was the apparent over prescribing of OxyContin. Despite the manufacturer's recommendation that dosing should occur over a 12-hour period, in many of the 27 cases, prescriptions were found for the administration of OxyContin 3,4 and even 6 times a day."* [48] (emphasis added).

E. Review of the Medical Literature

The conclusion that current warnings in the drug's labeling are inadequate to inform prescribers and, ultimately, patients, of specific information related to the potential for side effects and adverse reactions due to dosing frequencies of OxyContin in excess of the recommended q12h is highlighted by the fact that even medical journals mistakenly reported that the "suggested" or "suitable" dosing schedules for OxyContin were "q8-12." The following are among the articles maintained in PPLP's files that were produced to Petitioner pursuant to this investigation and which contained such misinformation:

- Pappagallo, M., M.D., *Aggressive Pharmacologic Treatment of Pain,* Pain Management in the Rheumatic Diseases (February 1999). In the article, the author states that the "recommended opioid preparations and dosing schedules" for OxyContin are "q8-12h po";

- *Considerations for Acute Pain Management in Ambulatory Orthopedic Surgery*, Orthopedic Special Edition (2000). The article identifies the suggested initial dosing for "[o]xycodone controlled release" is "10mg q8-12h"; and

- Cherry, N., M.B.B.S., *New Strategies in Opioid Therapy for Cancer Pain*, The Journal of Oncology Management (Jan./Feb 2000). The article states "[w]ith the approval of a controlled-release formulation suitable for 8-12 hour dosing, oxycodone has become a viable alternative to controlled-release morphine."

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[48] Anderson, D., Fritz, K. and Muto, J., *Postmortem Case Examples Involving OxyContin* (2001). This report was received by PPLP on October 3, 2001 and produced to Petitioner pursuant to its investigation.

The evidence of the significant incidence of prescriptions of OxyContin at more frequent dosing intervals than the package insert recommends, and the misunderstandings identified and discussed in PPLP's internal documents and noted in medical journals, demonstrates that current methods of informing physicians and patients are insufficient. PPLP's documents suggest that in determining the suitable dosing frequency for long-acting opioids, many prescribers are unsure of the distinction between the drug's delivery system and its elimination half-life. Moreover, many of these prescribers are confusing MS-Contin's dosing schedule (q8h – q12h) with OxyContin's, which should be administered, according to Robert Reder, M.D., PPLP's Vice President of Medical Affairs and Worldwide Drug Safety, "**exclusively** on a q12h dosing schedule." (emphasis added)[49] Indeed, during its presentation to its sales personnel in the winter of 2002, the company's sales and marketing executives suggested that physicians are incorrectly "thinking" OxyContin has the "[s]ame delivery system as MS Contin" in those instances "when they switch patients from q12h dosing of OxyContin to q8h" dosing.[50] Another version of the presentation comments in the annotation that "physicians see the delivery of OxyContin as the same as MS Contin. We can't have this."[51]

F. Dosing Outside the Recommended Guidelines May Contribute to the Illicit Supply of OxyContin

The OxyContin label changes in the summer of 2001 stem largely from the FDA's serious concern in April, 2001 about the "recent upsurge . . . of OxyContin abuse and diversion . . .."[52] This trend of abuse and diversion has not abated and, despite the labeling changes and

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[49] Reder, R., M.D., *Opioid formulations: tailoring to the needs in chronic pain,* European Journal of Pain (2001).
[50] *OxyContin q12h Workshop.*
[51] *Id.*
[52] The comments were made at a meeting held between the FDA and representatives of PPLP on April 23, 2001. FDA Meeting Minutes of FDA/PPLP Meeting, April 23, 2001.

increased regulatory scrutiny, continues to threaten not only the State of Connecticut,[53] but the entire United States.[54] While off-label dosing of OxyContin is certainly a patient safety issue, increased dosing frequency may also contribute to the abuse and diversion of OxyContin.

PPLP's internal documents agree with this assertion. At its national sales meeting held March 4-5, 2002, a PPLP document warned that "in one state roughly 26% of the Medicaid patients were on q8h dosing. *The extra dose may be an opportunity for diversion.*" (emphasis added).[55] Another internal document stressed that "[p]roper dosing minimizes abuse and diversion."[56] And a document used in presentations to sales staff entitled "How is OxyContin Being Dosed?" observed that "[t]he third [q8h], fourth [q6h], etc. doses are potentially being diverted."[57] The document specifies, by physician practice type, the percentage of prescriptions written with dosing frequencies that exceed PPLP's recommended guidelines, and emphasizes that this overall percentage "equates to 26,672 prescriptions per week" being written off-label for OxyContin.[58]

Thus, in PPLP's own words, prescribers dosing more frequently than twice a day potentially - - even if unknowingly - - contribute to an illicit supply of OxyContin. If the pain is adequately controlled at q12h, as PPLP claims, there is a tremendous incentive for an unscrupulous pain patient to divert the extra daily dose and sell it on the black market. The Drug Enforcement Administration estimates the street price for OxyContin at about $1 per milligram,

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[53] A July 2003 report from the National Drug Intelligence Center warns that "[t]he diversion and abuse of oxycodone products - - especially OxyContin . . . are increasing threats to Connecticut." *Connecticut Drug Threat Assessment – Update,* National Drug Intelligence Center, U.S. Dept. of Justice, p.25 (July 2003) (hereinafter, "*Connecticut Drug Threat Assessment*").

[54] The Drug Enforcement Administration's Office of Diversion Control issued another report on OxyContin diversion and abuse as recently as May, 2003.

[55] *Minimize Abuse/Diversion of OxyContin.*

[56] *OxyContin q12h Workshop.*

[57] *Id.*

[58] *Id.*

meaning one 80mg OxyContin is worth $80 on the street.[59] In other words, someone prescribed OxyContin at q8h would have one extra 80mg pill a day and could make over $29,000 a year selling the extra dose.

G. PPLP's Response to the q8h Problem

PPLP's package insert and marketing materials stress that OxyContin is recommended only for q12h dosing. Within its package insert (not in bold type) is the statement that if the pain is not controlled, it is appropriate to increase the dose, "not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h."[60] All the information in the insert referencing patient population, use, precautions, side effects and adverse reactions are pegged, therefore, to q12h dosing. In discussing the q12h issue with its sales staff in the winter of 2002, company executives reiterated that q12h dosing is "what is best for the patient."[61]

Despite these cautionary statements, PPLP has information that its drug is being prescribed outside the recommended dosing guidelines and, apparently based on its internal documents, has developed some information that such prescribing could have potentially harmful consequences. According to these documents, PPLP is concerned about the potential for increased side effects resulting from the more frequent administration, and the potential for illicit diversion of the "extra dose."

In response to these concerns, PPLP has undertaken two steps, but neither has been effective to disseminate this critical information to either the FDA or the healthcare community. First, in its labeling PPLP says: do not increase the dosing because we have no clinical information on dosing intervals shorter than q12h. But this statement does not affirmatively warn healthcare providers that increasing a patient's total daily dose of OxyContin by increasing

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[59] *Connecticut Drug Threat Assessment*, p.25.
[60] OxyContin™ package insert. ©2001 Purdue Pharma L.P. Stamford, CT 06901.
[61] *OxyContin q12h Workshop.*

the number of doses rather than increasing the q12h dose, may alter the stated side effect profile, cause an increase in the plasma concentrations of oxycodone and raise the risk of euphoria and sedation - - especially when the company has data that providers are not heeding the package insert and are prescribing at q8h or more frequently. Second, rather than issue a "Dear Healthcare Professional" letter, Safety Alert or revise the OxyContin labeling to make this information explicit, PPLP has instructed its sales representatives to "refocus" physicians *if* the representative learns the physician is prescribing more frequently than q12h.[62] *If* is the operative word because, during Petitioner's interviews conducted with former PPLP salesmen, one stated that sales personnel actually learn whether a physician is prescribing q8h or more frequently only when the physician voluntarily informs the salesperson of the practice; otherwise sales personnel do not know and do not affirmatively inquire.

It is unclear to what extent PPLP can access data that identifies specific physicians who prescribe the drug outside the recommended dosing guidelines, or whether its dosing frequency information is more general, but it appears that the sales representatives only learn of it if they happen to be told by the individual physician.

Relying on sales representatives is not an effective response for two reasons. First, sales representatives may only become aware of a fraction of physicians prescribing more frequently than q12h. Second, PPLP's commission structure pays its sales personnel a salary plus bonuses based on a specific percentage of net dollar sales of several PPLP products, including OxyContin, and a percentage of sales growth over the detail person's annual quota, with the focus on OxyContin sales. According to the sales personnel Petitioner interviewed, a salesman's

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[62] PPLP instructed its sales personnel when learning a physician prescribed q8h or more frequently to respond "[t]hat's great doctor, you're titrating and increased the dose of OxyContin by 50%. I wish all the doctors I call on were willing to do what you did. Let me share with you how you can accomplish the laudable goal of managing pain but continue dosing q12h." *OxyContin q12h Workshop*.

failure to achieve quota could result in counseling and/or termination from the company; hence there is pressure to continually increase sales. Sales representatives have an obvious disincentive to counsel physicians against more frequent prescribing when the result may be a decline in the sales representative's overall bonus or other adverse action. PPLP executives recognized the inherent flaws in the strategy of using commissioned salespersons to spread the word against prescribing OxyContin in excess of recommended guidelines by cautioning them not to "let the short term gain [from increased prescriptions] interfere with [PPLP's] long-term goal."[63]

PPLP's documents confirm that PPLP was aware of the incidence of prescriptions written for q8h or more frequently before it revised its labeling in the summer of 2001. The company's statistics for q8h prescribing in 1999 and 2000 were 12.1% and 14% respectively, and the PPLP document identifying that 351,000 prescriptions were "dosed q8h or shorter," constituting 19.5% of OxyContin prescriptions, notes that the data was based on IMS Health's data for the week ending May 4, 2001.[64] That is over two months before the company issued its revised labeling and only two weeks after it began meeting with the FDA to begin the process of revising the labeling - - which was allegedly motivated by a desire to educate prescribers on appropriate use of OxyContin, find ways to stem abuse and diversion, and make the use of the product safer. PPLP's Chief Executive Officer Michael Friedman testified before a congressional subcommittee investigating OxyContin abuse that the company usually receives IMS Health data between "six to eight weeks" after the prescription is written.[65] Therefore, PPLP likely had access to this specific information before the final revisions to its labeling. Indeed, the internal PPLP sales presentation "OxyContin q12h Workshop", which emphasizes the potential for

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[63] *OxyContin q12h Workshop.*
[64] *Id.*
[65] Testimony of Michael Friedman. *OxyContin: Its Use and Abuse.* Hearing before the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce. House of Representatives August 28, 2001.

increased side effects and diversion caused by dosing the drug q8h or more frequently, is dated July 25, 2001[66] - - **the same date as the FDA's approval of the revisions to the label.**[67]

Nevertheless, regardless of whether PPLP received this information in time to digest and include it in the July 2001 label revision, the question in this Petition is whether the company has taken adequate steps since then to expressly alert the healthcare community. The company has limited its warning efforts to the individual physician by physician approach, which has proved inadequate. PPLP has not attempted to explicitly or expressly communicate the warning to ***all*** prescribers of the potential health consequences and increased diversion inherent with more frequent dosing intervals, including those who continue their off-label prescribing practices without informing PPLP. These physicians PPLP has not yet identified, and may never identify.

IV. STATEMENT OF LEGAL GROUNDS

The Federal Food, Drug and Cosmetic Act (the "Act"), 21 U.S.C. §§ 301 *et seq.*, vests the FDA with the regulatory authority and responsibility for ensuring the safety of all marketed medical products. The Act is a safety statute, *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 487 (1996), whose primary objective is the protection of public health through the regulation of certain medical products moving in interstate commerce. *United States v. An Article of Drug, Bacto-Unidisk*, 394 U.S. 784, 798 (1969); *United States v. Vital Health Products, Ltd.*, 786 F. Supp. 761, 766-767 (E.D. Wis. 1992). Pursuant to its charge to protect the public health, the FDA has promulgated regulations detailing specific requirements for the labeling of prescription drugs, 21 C.F.R. § 201.57, as well as periodic postmarketing manufacturer reporting requirements to enable the agency to identify adverse event signals that may be linked to a specific

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[66] *OxyContin q12h Workshop.*

[67] FDA Approval Letter (July 25, 2001). Available at: http://www.fda.gov/cder/drug/infopage/oxycontin/default.htm

pharmaceutical. 21 C.F.R. §§ 314.80 and 314.81.[68] Among the labeling requirements are specific information the manufacturer is required to include in the drug's labeling, including information pertaining to warnings, precautions, adverse reactions, special instructions concerning at-risk populations, and the proper dosage and administration of the drug. 21 C.F.R. § 201.57. FDA labeling regulations are deemed minimum standards and drug manufacturers can add more stringent warnings without agency approval. *See Bell v. Lollar*, No. 22A01-0212-CV-475, 2003 Ind. App. LEXIS 1250, at *12 (Ind. App. July 17, 2003).

The Act prohibits the introduction into interstate commerce of any drug that is misbranded. 21 U.S.C. § 331(a). A drug shall be deemed to be "misbranded" if its labeling[69] is "false or misleading in any particular." 21 U.S.C. § 352(a). This provision of the Act applies regardless of whether the drug is sold over-the-counter or dispensed on prescription. *Pharmaceutical Manufacturer's Assoc., et al. v. FDA, et al.*, 484 F. Supp. 1179, 1185-1186 (D. Del. 1980). In determining whether a drug's labeling is misleading, and hence misbranded, the agency shall take into account, among other things:

> not only representations made or suggested by statement, word, design, device, or any combination thereof, but also the extent to which the labeling . . . fails to reveal facts material in the light of such representations or material with respect to consequences which may result from the use of the article to which the labeling . . . relates under the conditions of use prescribed in the labeling . . . thereof or under such conditions of use as are customary or usual.

21 U.S.C. § 321(n). This section of the Act pertains not only to misleading affirmative claims, but also to material omissions as well. *See Pharmaceutical Manufacturer's Assoc.*, 484 F. Supp. at 1184-1185 (noting that the Act's scope is not limited to misleading affirmative claims, but

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[68] Postmarketing adverse drug experience surveillance is intended to obtain information on rare, latent or long term drug effects not identified during premarket testing. Compliance Program Guidelines, Center for Drug Evaluation and Research, FDA, Ch. 53 (September 1999).

[69] A drug's labeling includes "all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce." 21 C.F.R. § 1.3(a). The definition applies to a drug's package insert.

requires "disclosure" of material facts "with respect to 'consequences which may result from the use' of the drug"). *See also* 21 C.F.R. § 1.21(a).

Prescription drug "[p]roduct warnings are intended for the physician, 'whose duty it is to balance the risks against the benefits' of various treatments and to prescribe the treatments he or she thinks best." *Martin v. Hacker*, 628 N.E.2d 1308, 1311-1312, 607 N.Y.S.2d 598 (1993). The drug manufacturer discharges its duty to convey adequate warnings by "providing the physician with sufficient information concerning the risks" of the drug. *Sita v. Danek Medical, Inc.*, 43 F. Supp.2d 245, 259 (E.D.N.Y. 1999). The duty to warn physicians of a drug's risks are particularly important because such dangers are not open and obvious. *Tampa Drug Co. v. Wait*, 103 So.2d 603, 607 (Fla. 1958). A manufacturer is deemed to be an expert in its drug and is under a "continuous duty . . . to warn physicians of the dangers incident to prescribing the drug, to keep abreast of scientific developments touching upon the manufacturer's product and to notify the medical profession of any additional side effects discovered from its use." *Schenebeck v. Sterling Drug Inc.*, 423 F.2d 919, 922 (8th Cir. 1970).[70] Hence, the issue with respect to the adequacy of a drug's warnings hinges on "whether the manufacturer[] met [its] duty of promulgating label warnings commensurate with [its] actual knowledge gained from research and adverse reaction reports as well as commensurate with [its] constructive knowledge as measured by scientific literature and other means of communication." *Dalke v. Upjohn Co.*, 555 F.2d 245, 248 (9th Cir. 1977).

As discussed in the Statement of Factual Grounds, above, PPLP has expressed concern internally that many prescribers were prone to increase OxyContin's dosing frequency because

[70] In addition to its duty to notify prescribers of updated safety information, FDA regulations also require the manufacturer to make periodic postmarketing reports to the FDA concerning issues related to adverse drug experiences, 21 C.F.R. § 314.80 and "significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product." 21 C.F.R. § 314.81.

they incorrectly based their decisions on the drug's stated elimination half-life and misunderstood the drug's delivery system. PPLP knew as early as 1998 that almost 13% of all prescriptions written for OxyContin were off-label, involving dosing frequencies that were in excess of the drug's recommended guidelines. Further, PPLP knew that the percentage of prescriptions written off-label in this manner continued to climb in succeeding years to almost 25% for the 80mg dose in 2000 and an amount approximating 20% of all prescriptions in the years 2001-2002. PPLP also knows - - or should know - - that even those percentages may underestimate the true percentage of practitioners prescribing OxyContin q8h or more frequently, especially in the higher dosage strengths.[71] In fact, in light of the *Journal of Managed Care Pharmacy* study, it appears that q8h is closer to the normal or usual prescription for OxyContin than PPLP's q12h recommended guideline.

In addition to knowing the rate of off-label prescribing, PPLP was sufficiently concerned to warn its sales personnel that such prescribing behavior will cause "overlapping blood levels," an "unacceptable" practice that "*will* increase blood levels thereby increasing the risk of side effects such as euphoria and sedation." (emphasis added). Thus, PPLP had knowledge of the material fact of additional side effects a patient might experience as a result of the off-label prescribing. *See* 21 U.S.C. § 321(n). Yet despite the company's knowledge of how prescribers were improperly prescribing its drug, and its apparent "actual knowledge gained from research and adverse reaction reports," *Dalke*, 555 F.2d at 248, that such prescribing posed potential additional risks to patients, PPLP has not, either as part of the revisions to its labeling in July, 2001 or since, communicated to all prescribers through its labeling or some other equally effective means that the side effect profile and other warnings contained in its package insert did

[71] *See, infra* footnotes 17 and 18, suggesting that a much higher percentage of prescriptions for OxyContin are actually written q8h or more frequently.

not adequately present the risks of side effects when the drug was prescribed q8h or more frequently.[72] Instead, PPLP retained the language from its earlier (pre July, 2001) package insert that physicians should not increase "the dosing frequency" because there is no "clinical information on dosing intervals shorter than q12h." The package insert further continues to assert that the elimination half-life is 4.5 hours and that it is appropriate it to adjust the dosage every 1 to 2 days, despite the company's acknowledgement to the Petitioner on November 17, 2003 that the actual apparent elimination half-life is 10 hours.

The facts uncovered and developed pursuant to Petitioner's investigation are analogous to those presented in *Ezagul v. Dow Chemical Corp., et al.,* 598 F.2d 727 (2d Cir. 1979). There, plaintiffs appealed the dismissal of their suit brought against a number of entities, including Parke Davis Company, the manufacturer of Quadrigen, a vaccine developed to protect against several diseases, including polio and whooping cough. At the time Quadrigen was developed, all vaccines packed in multidose vials required a preservative to maintain their sterility. Parke Davis used the preservative Phemerol in its manufacturing process to maintain Quadrigen's sterility. Subsequent to the drug's approval, however, postmarketing research indicated that Phemerol caused certain endotoxins to leak out of the vaccine and cause a fever, which could lead to convulsions and brain damage. *Id.* at 731. In addition to the postmarketing research, Parke Davis' own research personnel were "on record" as believing that the leakage of endotoxins was responsible for a "measured increase in adverse medical reactions associated" with the drug. *Id.* at 731-732.

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[72] As part of its negotiations concerning its labeling revisions in July, 2001, PPLP agreed to submit a Risk Management Program ("RMP") for OxyContin to the FDA. A proposed RMP was submitted on August 3, 2001. The purpose of the RMP was "to help ensure the safe use" of OxyContin. PPLP Proposed RMP. Despite this stated purpose, the RMP does not discuss - - *at all* - - the issue of prescribing q8h or more frequently, although PPLP agrees in the RMP to provide periodic reports to the FDA concerning, among other things, the "[r]ate of off-label use or inappropriate prescribing." PPLP Proposed RMP. PPLP has provided no evidence to the Petitioner that it has informed the FDA of this issue.

Nevertheless, even though armed with this information, Parke Davis continued to ship Quadrigen along with a package insert that stated the incidence of side effects following the drug's administration was "mild" and "no greater than is normally experienced" with a similar Parke Davis vaccine. *Id.* at 732. In analyzing the issues raised on appeal, the Second Circuit closely followed the reasoning of a similar case brought against Parke Davis in the Eighth Circuit, *Parke-Davis & Co. v. Stromsodt,* 411 F.2d 1390 (8th Cir. 1969). In *Stromsodt*, the Eighth Circuit held that the warning in the Quadrigen package insert failed to adequately apprise prescribers of hazards attendant with its use, and concluded that "[t]o tell the practitioner who had successfully used [the earlier vaccine] that reactions from Quadrigen are usually no greater . . . simply does not comport with the record facts . . . [;] and the knowledge of the medical experts associated with Parke-Davis and others . . ." is a response that is "inadequate in light of the frequency and severity of adverse reactions" associated with the drug and reported to the company. *Ezagul,* 598 F.2d at 732 (citing *Stromsodt,* 411 F.2d at 1400).

Using *Stromsodt* as precedent, the Second Circuit reviewed the record evidence presented against Parke Davis in *Ezagul*. According to the court, that evidence "strongly" suggested that Parke Davis continued to market Quadrigen although "fully cognizant" that sale of the drug would impose a risk of harm on patients who used the drug. *Ezagul*, 598 F.2d at 733. In reaching that conclusion, the court pointed to several exhibits from the record including internal company memoranda confirming specific undisclosed adverse reactions with the use of the drug and a myriad of outside communications from healthcare professionals notifying the company of adverse reactions encountered by their patients using Quadrigen. *Id.* As a result, the court held that Parke Davis' failure to disclose its "knowledge of special risks of harm attendant upon normal use," while continuing to posit in its package insert that only slight risks were attendant

with its use, were misleading and, thus, amounted to a misbranding of the drug in violation of section 352 of the Act. *Id.*

Applying the reasoning of the Eighth and Second Circuits, OxyContin's labeling may be considered "misleading," and the drug "misbranded," as those terms are used in the Act. 21 C.F.R. § 331(a). Like Parke Davis' labeling of Quadrigen, the labeling for OxyContin does not convey the potential risks of prescribing the drug in dosing frequencies that exceed the recommended guidelines, even though PPLP is aware that prescribing q8h or more frequently is an increasingly common practice that in certain circumstances will lead to elevated blood levels of oxycodone and, consequently, increased side effects. Also, like the Parke Davis package insert, PPLP states in its OxyContin package insert that there is no *"clinical information on dosing intervals shorter than q12"* (emphasis added), despite its knowledge from various sources of "special risks of harm attendant" from this prescription dosing schedule. *Ezagul*, 598 F.2d at 733. Telling practitioners in the OxyContin package insert that euphoria was reported in between 1% and 5% of patients involved in the clinical trials, and asserting that there is no "*clinical information on dosing intervals shorter than q12h,"* simply does not convey the full extent of the facts evidently known to PPLP from its own postmarketing studies, its knowledge from the MEDWATCH reporting system and its own scientific research. Finally, recommending that dosage adjustment is appropriate after one day may not be accurate if the true elimination half-life for OxyContin is 10 hours, as stated by PPLP recently, rather than the 4.5 hours stated on the label. If 10 hours is the more accurate representation of the elimination half-life, steady-state may not be reached for **two to four days**, meaning dose titration, followed one-day later by another dosage adjustment, may be a cause of significant accumulation of the drug and may increase the potential for risk of adverse reactions.

Although PPLP educated its sales personnel about the risks posed by prescribing OxyContin q8h or more frequently, it omitted some of the very same information in the OxyContin package insert. This omission, and the potentially serious consequences, requires immediate and wide-spread disclosure to all prescribers of the material fact regarding the potential risks that are not "open and obvious," *Tampa Drug Co.*, 103 So.2d at 607, to the prescriber and ultimately the patient. Fully informing health practitioners of the full extent of the risks is critical to the careful risk/reward balancing process a prescriber undergoes when considering the use of any prescription drug, especially one as powerful as OxyContin.

Even if the OxyContin labeling is not considered "misbranded" in contravention of the Act's prohibition against misleading information, PPLP has a responsibility to update and inform health professionals of the potentially serious and pressing safety issues accompanying the use of its drug. A drug's warning, to be adequate, "must be accurate, clear and consistent on its face and portray with sufficient intensity the risks involved in taking the drug," *Martin*, 628 N.E.2d at 1312, "particularly where the warning was qualified or lacked a sense of urgency." *Williams v. Lederle Laboratories, Div. of American Cyanamid Co.*, 591 F. Supp. 381, 385 (S.D. Ohio 1984). If a drug's labeling is deficient in advising health professionals of newly discovered latent risks, the FDA can initiate various actions, with or without the acquiescence of the manufacturer, including the action requested by Petitioner, such as a labeling change or a manufacturer's "Dear Healthcare Professional" letter, an FDA Safety Alert, Public Health Advisory, Talk Paper or Urgent Notice.[73]

There has been no sense of urgency in disseminating safety-related information pertaining to the growing practice of off-label prescribing of OxyContin, even though the

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[73] *See The Clinical Impact of Adverse Event Reporting,* Center for Drug Evaluation and Research, FDA (October 1996).

potential risks are increased through this prescribing practice. FDA regulations provide a means for a manufacturer to expedite label changes before seeking agency approval in order to disseminate important safety information when new risk information surfaces. 21 C.F.R. § 314.70(c)(2). The regulations specifically allow manufacturers to make changes that, among other things, "strengthen a ... warning, precaution, or adverse reaction ... or add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product." *Id.* The purpose of the regulations is obvious. They envision that information may arise after a drug is approved for marketing, which "in the mind of the manufacturer, calls into question the current safety of the drug ... and calls for a strengthened warning ... on the manufacturer's own initiative." *Caraker v. Sandoz Pharms. Corp.*, 172 F. Supp.2d 1018, 1033-1034 (S.D. Ill. 2001).

Rather than revise its labeling or issue a Safety Alert, PPLP has relied on its campaign by sales personnel to "refocus" individual physicians - - *if* they learn of their off-label OxyContin prescribing pattern. These personnel have a personal financial disincentive - - indeed a self-interest in not advising the prescriber - - that makes this method at least highly questionable in its efficacy and consistency. The inadequate nature of the label warnings are of special concern since PPLP, based on its own internal documents, is concerned that there is a causal connection between prescribing OxyContin q8h or more frequently and the increased occurrence of side effects. *See Salmon v. Parke, Davis & Co.*, 520 F.2d 1359, 1363 (4th Cir. 1975) (finding a jury could have inferred that the manufacturer's warning was diluted and lacked the emphasis that the danger demanded where the warning did not unequivocally state that there was a causal connection between its drug and the resulting side effect). By failing to act in a reasonable manner, PPLP has breached its obligation to warn health professionals. *Caraker*, 172 F. Supp.2d

at 1033. *See also Edwards v. Basel Pharms.*, 933 P.2d 298, 302 (Okla. 1997) (concluding that a drug manufacturer's compliance with the FDA's minimum standards for warnings "does not necessarily complete the manufacturer's duty") (citation omitted); *Savina v. Sterling Drug, Inc.*, 795 P.2d 915, 931 (Kan. 1990) ("Regulations imposed by the FDA are minimal standards. A drug company is not prohibited from providing additional warnings and additional information that is not required by the FDA.")

Under relevant law, OxyContin may be considered "misbranded" within the meaning of the Act because information contained in the drug's labeling fails to fully disclose potential risks incident to prescribing OxyContin q8h or more frequently and inaccurately describes the incidence of side effects and adverse reactions when the drug is so prescribed. The drug may also be considered "misbranded" because the label states its elimination half-life to be 4.5 hours, when PPLP has now indicated to the Petitioner that the half-life is actually approximately 10 hours. Thus, the FDA will be acting within its mandate, as well as in the public interest, by granting this Petition.

V. PETITIONER'S REVIEW OF INFORMATION RECENTLY PROVIDED BY PPLP

The Petitioner has met with senior executives from PPLP on three occasions since September 8, 2003 to discuss the Petitioner's concerns with respect to the information it developed through its investigation. As a result of these meetings, PPLP voluntarily provided additional information to the Petitioner. Because PPLP has designated this information confidential, it cannot be included with this Petition.

Petitioner has reviewed all of the information and documents PPLP provided at or subsequent to the meetings with company officials. The information does not alter Petitioner's concerns as expressed in this Petition. On the contrary, the additional documents and

information PPLP has provided further supports: (1) that a relatively large percentage of prescriptions for OxyContin were prescribed in dosing frequencies in excess of the company's recommended guidelines, (2) that additional information related to the proper dosing frequency of OxyContin was not provided to healthcare professionals unless a prescriber made a specific request for such information, and that such information did not expressly communicate that prescribing the drug q8h or more frequently increased the potential for side effects or diversion, (3) that PPLP continued to stress to its sales representatives, on several occasions and in different venues, its own concerns that prescribing q8h or more frequently raised the risks of side effects and diversion and was due, in part, to prescribers' lack of education with respect to using controlled-release opioids and a general confusion about the differences between MS-Contin and OxyContin and, (4) that in actuality, the elimination half-life of OxyContin was closer to 10 hours rather than the 4.5 hours identified in the drug's label.

VI. CONCLUSIONS AND RECOMMENDATIONS

Controlled substances such as OxyContin are vitally important medicines for the hundreds of thousands of patients who experience substantial pain. Because of their power, opioid analgesics can provide important pain relief, but they also may raise potentially serious risks. Manufacturers have a legal and moral responsibility to disseminate the most current safety-related information to ensure that each prescriber has full knowledge of the risks and prescribes accordingly. The FDA recognized early that controlled-release dosage form drugs, like OxyContin, pose a risk of unsafe overdosage if the active ingredients in the drug are released

"over too short a time interval."[74] Petitioner's investigation has demonstrated this precise risk exists when OxyContin is prescribed q8h or more frequently in the manner discussed in this Petition.

Since this information has not been disseminated effectively to prescribers or the public, Petitioner urges the Commissioner to take immediate action to ensure that the risks of misuse are fully disseminated to healthcare providers and the public.[75]

VII. ENVIRONMENTAL IMPACT

Petitioner believes the action requested in this Petition has no significant environmental impact.

[74] *Compliance Policy Guides*, Office of Regulatory Affairs, FDA, § 460.700 (1987).
[75] In the event generic versions of the drug become available for sale, we ask that the same prescribing information and warnings be required of the generic drug manufacturers as well.

CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

Respectfully submitted,

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